REMARKS

I. Status Summary

Claims 1-12 and 45-54 are pending and have been examined by the United States Patent and Trademark Office (hereinafter "the Patent Office"). Claims 1-12 and 45-54 presently stand rejected.

Claims 1-12 and 45-54 have been rejected under the enablement provision of 35 U.S.C. § 112, first paragraph.

Claims 1-12 and 45-54 have been rejected under 35 U.S.C. § 112, second paragraph upon several bases.

Claims 1, 2, 4-7, 11, 12, 45, 46, and 48-51 have been rejected under 35 U.S.C. § 103(a) upon the contention that the claims are unpatentable over Kunzelmann-Marche *et al.* (2001) 276 *J Biol Chem* 5134-5139 (hereinafter "Kunzelmann-Marche") in view of U.S. Patent Application Publication No. 2002/0165353 of Malouf *et al.* (hereinafter "Malouf").

Claims 1, 4, 5, 11, 12, 45, and 49 have been amended. Support for the amendments to the claims can be found throughout the specification as filed, including particularly at page 17. line 20, to page 18, line 5; Examples 4-6 (platelet VDCC comprising a VDCCα1 subunit polypeptide); and Examples 7-9 (platelets as test samples comprising VDCCα1 subunit polypeptides). Additional support can be found in Examples 7-9 (calcium transport is associated with phosphatidylserine exposure and platelets in culture as test samples). Thus, no new matter has been added by the amendments to the claims.

Reconsideration of the application as amended and in view of the following remarks is respectfully requested.

II. Response to the Rejection under 35 U.S.C. § 112, First Paragraph

The Patent Office has rejected claims 1-12 and 45-54 under 35 U.S.C. § 112, first paragraph, upon the contention that the claims are not enabled. Specifically, the Patent Office contends that the test sample in the instant claims does not require that the platelet VDCC polypeptide be present in a cell membrane, nor does it require that cellular constituents required for phosphatidylserine (hereinafter "PS") exposure on the

surface of the cell be present. The Patent Office further contends that without these cellular constituents, step (c) of claim 1 would not measure anything.

After careful consideration of the Patent Office's rejection and the basis therefore, Applicants respectfully traverse the rejection and submit the following remarks.

Initially, applicants respectfully submit that in analyzing enablement, the Patent Office must considered the claims from the perspective of one of ordinary skill in the art after review of the specification as a whole. When this is done, applicants respectfully submit that after review of the instant specification, one of ordinary skill in the art would understand that the biological activity disclosed in the specification to correlate with phosphatidylserine (PS) exposure on the surface of platelets comprises calcium transport activity. Given this perspective, applicants respectfully submit that after review of the instant specification, one of ordinary skill in the art would thus understand that the test sample comprising the platelet VDCCα1 subunit polypeptide provides for assaying calcium transport via the VDCC. Thus, applicants respectfully submit that one of ordinary skill in the art would understand the nature of the test samples as recited in claims 1 and 45.

Notwithstanding the above and in an effort to facilitate prosecution, claims 1 and 45 have been amended to recite *inter alia* that the test samples comprise platelet VDCCs comprising a VDCCα1 subunit polypeptide, wherein the test sample permits measuring calcium transport via the VDCC comprising the VDCCα1 subunit polypeptide. Claims 1 and 45 have been further amended to recite measuring an effect of the candidate substance on calcium transport via the VDCC comprising the VDCCα1 subunit polypeptide (claim 1) or an interaction, effect, or combination thereof, of the candidate substance on the test sample (claim 45). Support for the amendments can be found throughout the specification as filed, including particularly at page 17. line 20, to page 18, line 5; Examples 4-6; and Examples 7-9. Thus, no new matter has been added by the amendments to the claims. Applicants respectfully submit that in light of these amendments, the assertions presented by the Patent Office in support of the rejection of claims 1-12 and 45-54 with respect to the nature of the test samples and the activities to be assayed have been addressed.

Turning now to the instant rejection as applied to claims 5 and 6, the Patent Office asserts that the specification does not disclose a platelet in cell culture or a recombinant platelet, and further that there is no guidance on other cells or cell lines predictive of PS exposure in platelets. Applicants respectfully disagree.

Initially, applicants respectfully submit that Examples 7-9 all relate to experiments on platelets with respect to VDCC antagonists and correlations with PS exposure.

Furthermore, applicants respectfully submit that after consideration of the presently disclosed subject matter, one of ordinary skill in the art would understand that the subject matter of the instant application relates at least in part to calcium transport activity through the platelet VDCCα1 subunit, and that such transport can correlate with PS exposure. Therefore, it is believed that one of ordinary skill in the art would understand that a test sample can include a cell (*e.g.*, a platelet) that comprises a VDCC that itself can include a VDCCα1 subunit polypeptide.

Applicants further respectfully submit that one of ordinary skill in the art would also understand that many different types of cells express VDCCs, and that in order to test a VDCCα1 subunit polypeptide, any such cell can be transformed to express a VDCCα1 subunit polypeptide. For example, the instant specification on page 38, line 32 through page 39, line 15, clearly discloses recombinant cells including, but not limited to recombinant megakaryocytes and platelets (*see especially* page 39, lines 14-15), that have been transfected, infected, or adsorbed with a polynucleotide that encodes a biologically active platelet VDCC 1 subunit polypeptide (*see also* Section C. Introduction of Gene Products beginning on page 42 of the instant specification). Applicants thus respectfully submit that not only is it is entirely within the ability of one of ordinary skill in the art to produce such a recombinant cell and employ such a recombinant cell as a test sample, the instant specification explicitly discloses doing so.

Summarily, applicants respectfully submit that the instant specification discloses that calcium transport through a VDCC comprising a VDCCα1 subunit polypeptide is associated with PS exposure on platelets. Therefore, one of ordinary skill in the art would also understand that a candidate substance that has an effect on calcium transport through a VDCC comprising a VDCCα1 subunit polypeptide would also be

expected to have an effect on PS exposure on a platelet. As such, applicants respectfully submit that after review of the instant specification, one of ordinary skill in the art would be able to generate the test samples recited in claims 1-12 and 45-54 using no more than ordinary experimentation.

Accordingly, applicants respectfully submit that the instant specification fully enables claims 1 and 45. Furthermore, applicants respectfully submit that claims 2-12 and 46-54 all depend directly or indirectly from claim 1 or claim 45, respectively, and thus claims 2-12 and 46-54 are also believed to be enabled. As such, applicants respectfully request that the instant rejection of claims 1-12 and 45-54 under the first paragraph of 35 U.S.C. § 112 be withdrawn at this time.

III. Responses to the Rejections under 35 U.S.C. § 112, Second Paragraph

Claims 1-12 and 45-54 have also been rejected on several bases under the second paragraph of 35 U.S.C. § 112. Specifically, the Patent Office contends that claims 1, 3, 4, 7, 47, and 48 are indefinite.

After careful consideration of the Patent Office's rejections and the reasons therefor, Applicants respectfully traverse the rejection and offer the following remarks.

III.A. Response to the First Rejection

In the first rejection, the Patent Office asserts that the steps in claim 1 are inconsistent with the goals of the preamble. Applicants respectfully disagree. Claim 1 relates to methods for screening candidate substances for an ability to modulate PS exposure on the surface of a platelet. The specification discloses that PS exposure of the surface of platelets can correlate with the calcium transport activity of VDCCs comprising a VDCCα1 subunit. Applicants respectfully submit that any test sample that comprises a VDCCs comprising a VDCCα1 subunit can be employed in assaying calcium transport through said VDCC.

Therefore, applicants respectfully submit that the Patent Office's apparent assertion that the test sample must comprise a platelet is believed to be improper, and respectfully request that the instant rejection of claim 1 be withdrawn at this time.

III.B. Response to the Rejection of Claims 4 and 48

Next, the Patent Office asserts that claims 4 and 48 have been interpreted to mean that the nucleic acid molecule encoding the channel has been expressed to produce the VDCCα1 subunit polypeptides recited in the claims, but that it is also possible that the nucleic acid molecules and the VDCCα1 subunit polypeptides are discrete components of the test sample. Applicants have amended claims 4 and 48 to recite that test sample expresses a nucleic acid molecule encoding the platelet voltage dependent calcium channel (VDCC) α1 subunit polypeptide. Applicants thus respectfully submit that the instant rejections of claims 4 and 48 have been addressed.

III.D. Response to the Rejection of Claim 7

Claim 7 has been rejected upon the contention that the claim does not require that the calcium channel be present on the surface of the platelet or in any way associated with the platelet. Applicants respectfully disagree. Applicants respectfully submit that claim 7 depends from claim 1, which recites that the test sample (in some embodiments, a platelet) comprises a VDCC comprising a VDCCα1 subunit polypeptide, and further that the test sample permits measuring calcium transport via the VDCC comprising the VDCCα1 subunit polypeptide. Applicants thus respectfully submit that it is clear from claim 7 in view of claim 1 that the VDCCα1 subunit polypeptide is a component of the test sample.

Additionally, in view of the language of claim 7, which recites that the test sample comprises a platelet, applicants respectfully submit that after review of the instant specification, one of ordinary skill in the art would understand that to measure calcium transport via the VDCC comprising the VDCCα1 subunit polypeptide, the VDCC comprising the VDCCα1 subunit polypeptide must be present on the surface of the test sample (*i.e.*, the platelet). Accordingly, applicants respectfully submit that the instant rejection of claim 7 has been addressed.

III.D. Response to the Rejection of Claims 3 and 47

Next, the Patent Office asserts that claims 3 and 47 are confusing because the limitations set forth therein do not further modify the methods of claims 1 and 45. According to the Patent Office, the step of isolating a gene encoding the candidate

polypeptide does not further limit the method of screening candidate substances for their ability to modulate phosphatidylserine on the surface of a cell. Applicants respectfully disagree.

Initially, applicants respectfully submit that it is clearly contemplated in the instant specification to employ libraries of candidates (*see e.g.*, Specification at page 71, lines 24-32). In some embodiments, the libraries of candidates can be libraries of candidate polypeptides. In view of this, applicants respectfully submit that after review of the instant specification, one of ordinary skill in the art would understand that administering a candidate polypeptide in the form of a library (or library fraction) could lead to the discovery that one of the administered polypeptides present in that library could have an effect on calcium transport by the VDCC.

Further, the candidate polypeptide can be purified to homogeneity and re-checked for activity, thus confirming which of the candidate polypeptides present in the administered library or fraction thereof has the desired activity. One of ordinary skill in the art would understand that one way to purify the candidate to homogeneity would be to isolate the gene that encodes the candidate to produce the candidate in homogenous form. Given that libraries of polypeptides can be generated from expression libraries, one of ordinary skill in the art would understand how to perform the additional step recited in claims 3 and 47.

Accordingly, applicants respectfully submit that when claims 3 and 47 are interpreted from the perspective of one of ordinary skill in the art after reviewing the instant specification, such a skilled individual would understand how claims 3 and 47 include an additional element vis-à-vis claims 1 and 45, respectively. As such, applicants respectfully submit that claims 3 and 47 are proper dependent claims and further that they fully comply with the requirements of 35 U.S.C. § 112, second paragraph.

III.E. Summary

Summarily, applicants respectfully submit that the metes and bounds of the subject matter encompassed by claims 1, 3, 4, 7, 47, and 48 would be understood by one of ordinary skill in the art after review of the specification. Applicants further respectfully submit that 35 U.S.C. § 112, second paragraph requires no more, and thus

applicants respectfully request that the Patent Office withdraw the instant rejections of claims 1, 3, 4, 7, 47, and 48 at this time.

IV. Response to the Rejection under 35 U.S.C. § 103(a)

The Patent Office has rejected claims 1, 2, 4-7, 11, 12, 45, 46, and 48-51 under 35 U.S.C. § 103(a) upon the contention that the claims are unpatentable over Kunzelmann-Marche *et al*. in view of Malouf. According to the Patent Office, Kunzelmann-Marche teaches screening candidate substances for their ability to modulate phosphatidylserine exposure on the surface of a cell line that expresses receptors such as those found in platelets using flow cytometry. The reference is also asserted to disclose that Ca^{2+} channels in platelets would have been known to have been involved in phosphatidylserine exposure on the cell surface. The Patent Office concedes that the reference does not disclose the platelet voltage dependent calcium channel (VDCC) of SEQ ID NO: 2 that is encoded by the nucleic acid sequence of SEQ ID NO: 1, but asserts that this deficiency is cured by Malouf, which is asserted to disclose the platelet voltage dependent calcium channel (VDCC) of SEQ ID NO: 2 that is encoded by the nucleic acid sequence of SEQ ID NO: 1.

The Patent Office thus contends that it would have been obvious to screen candidate substances for their ability to modulate phosphatidylserine exposure on the surface of a cell line where the VDCC taught by Malouf was present. The Patent Office further contends that one would have been motivated to do so as Malouf discloses that this VDCC is found in platelets and Kunzelmann-Marche teaches that calcium mobilization involving platelet calcium channels is involved in phosphatidylserine exposure on the surface of the cell.

After careful consideration of the Patent Office's rejection and the basis therefor, applicants respectfully traverse the rejection and submit the following remarks.

The present rejection has been maintained from the previous Official Action. In response to said Official Action, applicants argued that the instant claims are entitled to the filing date of the parent application, which was published as Malouf, and thus Malouf cannot be considered prior art as to the instant claims.

Applicants respectfully reiterate that if Malouf is being relied on for its teaching of platelet VDCCα1 subunit biosequences and/or that platelets have a VDCC transporter, the Patent Office is believed to be in error in not permitting the instant application to claim priority back to the application that published as Malouf. Applicants respectfully submit that with respect to these aspects, the disclosure of the instant application and of the application that published as Malouf are identical. Therefore, applicants respectfully submit that they are entitled to the filing date Malouf for the present claims.

Furthermore, applicants argued in the previous response that instant claim 45 is the same as original claim 38 of Malouf. The Patent Office now asserts, however, that claim original 38 of Malouf recites "establishing a test sample comprising a nucleic acid molecule" (emphasis supplied), whereas instant claim 45 in its original form recited that the test sample comprised a polypeptide. Applicants respectfully submit, however, that one of ordinary skill in the art would understand that the nucleic acid molecule recited in original claim 38 of Malouf can be translated to produce the polypeptide of instant claim 45. The Patent Office's attention is directed to the discussion presented hereinabove in section *III.B.* in which applicants have clarified that the test sample can express the nucleic acid in order for candidate substances that modulate a biological activity (*e.g.*, calcium transport) of the VDCCα1 subunit polypeptide to be screened.

Given that the specification and claims of a patent application must be viewed from the perspective of one of ordinary skill in the art after consideration of the specification (*see* M.P.E.P. 2106: "USPTO personnel must always remember to use the perspective of one of ordinary skill in the art. Claims and disclosures are not to be evaluated in a vacuum"), applicants respectfully reiterate that instant claim 45 relates to the same subject matter as original claim 38 of Malouf.

Continuing with the instant rejection, applicants further respectfully submit that the Patent Office is believed to have misinterpreted the disclosure of Kunzelmann-Marche *et al.* in attempting to establish a *prima facie* case of obviousness of claims 1, 2, 4-7, 11, 12, 45, 46, and 48-51 over the combination of Kunzelmann-Marche *et al.* and Malouf. Particularly, applicants respectfully submit that Kunzelmann-Marche *et al.* do not assay calcium transport via the VDCC system, and thus there is no disclosure in Kunzelmann-Marche *et al.* to motivate one of ordinary skill in the art to believe that

VDCC-based calcium transport is involved in any biological activity in platelets including, but not limited to phosphatidylserine (PS) exposure.

To elaborate, the Patent Office's attention is directed to the DECLARATION OF TIMOTHY C. NICHOLS, M.D. PURSUANT TO 37 C.F.R. §1.132 (hereinafter "the Nichols Declaration) submitted herewith. The Nichols Declaration highlights several conclusions drawn by the Patent Office that are believed to be based on inaccurate interpretations of Kunzelmann-Marche *et al*.

First, Kunzelmann-Marche *et al*. does not disclose any investigations into VDCC-based calcium transport in platelets. Rather, Kunzelmann-Marche *et al*. discloses calcium transport via the store-operated Ca^{2+} entry (SOCE) system (*see* Item 5 of the Nichols Declaration). The SOCE system, which employs calcium channels referred to as store-operated Ca^{2+} channels (SOCCs), thus involves a distinct calcium transport system from the VDCC system disclosed in the instant application. Therefore, it is not possible to conclude from Kunzelmann-Marche *et al*. whether calcium transport via a VDCC system has any effect on PS exposure in any cell type.

Furthermore, Kunzelmann-Marche *et al*. does not employ platelets. Rather, Kunzelmann-Marche *et al*. discloses assays of calcium transport in human erythroleukemia (HEL) cells, which are from a malignant cell line. Applicants respectfully submit that malignant cell lines are known in the art to be of dubious use in predicting activities in "normal" cells such as platelets. The Patent Office's attention is directed to Items 9-12 of the Nichols Declaration, which describe how particularly with reference to VDCC transporters, experiments with malignant and/or transformed cell lines are not necessarily predictive of activities in corresponding non-transformed cells.

In fact, Item 11 of the Nichols Declaration specifically describes how data generated with a transformed cell line (*i.e.*, the MEG-01 cell line) that is closer in type to platelets than the HEL cell line employed by Kunzelmann-Marche *et al*. was rejected in peer review as being not necessarily predictive of VDCC activity in platelets. The relevant reviewer cited two references, copies of which are being submitted herewith as **Exhibits B** and **C**, which demonstrated expression of VDCC in malignant or transformed cells but not in the wild type cell of the same origin.

Therefore, applicants respectfully submit that as exemplified by this reviewer, those of skill in the art believed that various biological activities of transformed cell lines, including particularly calcium transport via the VDCC system, could be viewed as not predictive of similar activities being present in non-transformed cells. As a result, applicants respectfully submit that even if Kunzelmann-Marche *et al*. had been assaying VDCC-based calcium transport in the HEL cells, which applicants respectfully submit they were not, the results derived therefrom would not have given one of ordinary skill in the art a reasonable expectation that a similar activity would have been present in normal platelets.

Summarily, and as set forth in Item 13 of the Nichols Declaration, applicants respectfully submit that Kunzelmann-Marche *et al*. does not study VDCC-based calcium transport in platelets, provides neither evidence nor a suggestion that there is a VDCC system in platelets, and fails to suggest that the SOCE system in malignant cells is mediated by and/or associated with a VDCC biological activity. Therefore, applicants respectfully submit that Kunzelmann-Marche *et al*. in view of Malouf does not support a rejection of claims 1, 2, 4-7, 11, 12, 45, 46, and 48-51 under 35 U.S.C. § 103(a).

Accordingly applicants respectfully request that the instant rejection of claims 1, 2, 4-7, 11, 12, 45, 46, and 48-51 under 35 U.S.C. § 103(a) be withdrawn at this time. Applicants further respectfully submit that claims 1, 2, 4-7, 11, 12, 45, 46, and 48-51 under 35 U.S.C. § 103(a) are in condition for allowance, and respectfully solicit a Notice of Allowance to that effect.

CONCLUSION

In light of the above amendments and remarks, it is respectfully submitted that the present application is now in proper condition for allowance, and an early notice to such effect is earnestly solicited.

If any small matter should remain outstanding after the Patent Examiner has had an opportunity to review the above Remarks, the Patent Examiner is respectfully requested to telephone the undersigned patent attorney in order to resolve these matters and avoid the issuance of another Official Action.

DEPOSIT ACCOUNT

The Commissioner is hereby authorized to charge any deficiency in payment or credit any overpayment of fees associated with the filing of this correspondence to Deposit Account No. **50-0426**.

Respectfully submitted,
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